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PRINCIPAL INVESTIGATOR: Thomas Scalea, M.D.

CONTRACTING ORGANIZATION: University of Maryland, Baltimore
Baltimore, MD 21201

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14. ABSTRACT

This report represents the third year in a multi-year effort to improve outcomes in patients with traumatic brain injury (TBI) utilizing human and animal models. Year 1 focused on development of an infrastructure for gathering data in TBI patients, development of a protocol to advance understanding of the inflammatory process which follows TBI, and creation of a basic science model of brain trauma. Staff were hired and assigned, equipment purchased and protocols and databases developed.

Year 2 saw the implementation of two human use protocols, on-going development and testing of the Brain Resuscitation Registry (BRR) to provide structure and linkage capabilities for data collection and outcome reporting, and further development and re-formatting of the animal model sub-project.

Year 3 accomplishments included the ongoing enrollment of subjects in the human use protocols, development and implementation of 2 retrospective human use protocols, processing of specimens for the Cytokines sub-project, further development of the BRR and initiation of the basic science model including both small and large animal models of polytrauma. A one-year no-cost extension was granted in August 2010. This extension will allow completion of the current protocols as well as addition of 1 new human use protocol.

15. SUBJECT TERMS

Traumatic Brain Injury (TBI); vital signs; cytokines; pre-hospital care; polytrauma

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Table of Contents

INTRODUCTION

Traumatic Brain Injury (TBI) is the primary cause of trauma mortality in both civilian and military populations, a major source of long-term disability world-wide and a substantial independent cause of death in the U.S. The dominance of TBI in trauma epidemiology is due to our inability to treat primary central nervous system injury and the realization that the phenomenon of secondary brain injury (pathology at the metabolic, cellular, vascular and tissue levels) begins within seconds after the primary trauma and plays a profound role in the subsequent evolution of TBI.

The first phase of this multi-year effort to improve outcomes in TBI patients focused on developing the infrastructure necessary to associate elements of care for the TBI patient with specific and relevant outcomes, including establishment of a centralized Brain Resuscitation Registry for data capture, deployment of equipment to capture continuous pre-hospital and in-hospital vital signs, develop a protocol to examine the contribution of inflammatory cytokines after TBI and to develop an animal model of penetrating brain trauma.

Year 2 efforts focused on the implementation of two human use protocols, on-going infrastructure development and further development of the animal model sub-projects. The development of the Brain Resuscitation Registry (BRR), providing structure and linkage capabilities for human use data collection and outcome reporting, moved into the beta testing phase.

During Year 3 several sub-projects moved close to completion. Full implementation of screening and tracking functions of the BRR were achieved following the purchase of dedicated server and research computer tablets. With improvements in the matching and processing of vital signs data, 4995 subjects were enrolled and detailed analysis initiated. Enrollment for the Cytokines sub-project was completed, samples processed and preliminary analysis begun. Two new retrospective human use protocols were approved and initiated during Year 3 and 1 additional human use protocol developed with planned submission for IRB approval in October 2010. The animal use protocols continued refinement. The controlled cortical impact (CCI) device was finally purchased late in Year 3 for use in both the small and large animal models.

BODY

This is the annual report for Year 3 of a multi-year project. Table 1 below reflects the Project Milestones Timeline adjusted based on the actual funding award date of September 17, 2007. Start and finish date columns reflect target timelines while subsequent columns reflect actual task completion dates. Research progress is further summarized by the itemized Statement of Work Tasks following the table.

Table 1: Timeline

Activity name	Target Completion State Date	Target Completion Finish Date	Actual Completion
Patient recruitment and monitoring			
** IRB approvals	1-Oct-07	31-Jan-08	Vital signs 02-Apr-08 Cytokines 29-Jul-08 TBI &Fracture 29-Mar-10 TBI & O2 29-Mar-10
TCD and BAM	15-Sept-10	31-Jan-11	
** hiring and training of staff	1-Oct-07	31-Jan-08	
**design and implementation of data collection systems	1-Oct-07	31-Jan-08	
**patient enrollment	31-Jan-08		Cytokines 31-Jan-2010 Vital Signs On-going
**data collection	31-Jan-08		
**data collation and analysis	1-May-08		
cytokine laboratory			
**identification and training of staff	1-Oct-07		
**clinical data protocols	1-Oct-07		
animal model			
**IRB approvals	1-Oct-07		26-Feb-08
**final study design	1-Oct-07		

Implement plans for recruiting and monitoring patients.
Obtain Institutional Review Board (IRB) approval for recruiting and monitoring TBI patients.

All human sub-projects have received IRB approval from the University of Maryland (UMB), IRB and the USAMRMC ORP, HRPO.

Sub-project 1: Vital Signs Data in Trauma Patients

This project was initially approved by UMB, IRB and USAMRMC ORP, HRPO upon continuing review on 2/21/08. This study was then re-assigned to the current project "Early Support of Intracranial Perfusion," on 2/26/08.

During Year 1 several amendments were made to the project including a waiver of informed consent. The most recent annual renewal for this protocol was submitted to UMB IRB in December and approved for continuation on 12/07/09. The continuing review report was submitted to USAMRMC ORP, HRPO on 01/06/10.

Based on successful (99.2%) matching of the 2008 - 2009 STC admission vital signs data for patients fitting enrollment criteria, and the enrollment of 4995 subjects, an amendment will be submitted in early October 2010, to request the enrollment of an additional 9000 subjects, which will complete the 2010 admission year.

Sub-project 2: Early Support of Intracranial Perfusion – Cytokines

The protocol was initially submitted to UMB IRB on 3/20/08 and after requested revisions the final protocol was approved by UMB, IRB on 7/28/08 and USAMRMC ORP, HRPO on 7/29/08. The most recent annual renewal for this protocol was submitted to UMB IRB on 2/26/10 and approved for continuation on 3/18/09. The continuing review report was submitted to USAMRMC ORP, HRPO on3/31/10 and the acceptance memorandum received on 06/09/10.

New sub-projects for Year 3

Two new retrospective sub-projects were initiated in Year 3, in preparation for prospective studies. Both were approved by UMB IRB as exempt protocols on 02/24/10 and approved as exempt by USAMRMC on 03/29/10

Traumatic Brain Injury and Fracture Fixation

Traumatic Brain Injury, Oxygenation and Outcomes

New sub-project: Transcranial Doppler and Brain Acoustic Monitoring

At the end of Year 3, a protocol to evaluate two non-invasive tools for assessment of cerebral perfusion and vasospasm in patients with severe TBI was developed. This protocol will use both Transcranial Doppler (TCD) screening and the Brain Acoustic Monitor (BAM) to study the incidence of vasospasm in patients with severe TBI. Using well-established criteria for vasospasm detected with TCD, the BAM device data will be analyzed to determine the ability to apply this non-invasive bedside tool to improve diagnostic capabilities in patients with severe TBI. Forty patients with severe TBI will be enrolled in this pilot study. Daily TCDs and BAMs will be obtained for 7 days following injury. Dr Kevin Sheth will be joining the research team as a co-investigator for this study. The protocol will be submitted to UMB IRB in October 2010, and to USAMRMC once approved.

Complete the Brain Resuscitation Registry network architecture

During Year 1, secure web-based Trauma Registry containing clinical patient information for trauma patients was established. Year 2 focused on the continuing development of the network architecture. Links were established to automate the extraction of patient data needed to profile, enroll, manage and analyze current study populations. Study protocols were centralized and automated allowing for communication between studies to be established. Screens were added to the Registry for current trauma patients allowing selection and clinical data management. The Cytokines sub-project served as the test study for these processes and training of research staff.

Year 3 progress included the installation of a dedicated server which along with purchase of dedicated screening tablets has allowed the implementation of a fully active automated screening process. Screening of all TRU Patients is now tracked through the system. Addition of a minimum required data feature, ensures that key trauma data points are captured before the system will permit a patient to be closed out even if they are not suited for any study.

Adjustments to the rules module (and its interface) are finalized and it has been accurately filtering the required include/exclude criteria for the studies currently in the system. Development of security processes and user categories continue to develop. The system restricts users on a study-by-study bases and can permit view only roles or other access restrictions based on the users job responsibilities and study privileges. Reporting has continued to be developed. There are now real time screening stats on each study that provide information on how many relevant patients were screened and the breakdown of why candidates were ineligible for a particular study. Outcomes data capture is now in the early pilot phase. Trauma clinics have begun pilot testing the administration of standard outcomes surveys to every patient (ie. Rivermead, SF-12, etc). These surveys are administered on Scantron forms that can then be imported into the Brain Resuscitation Registry and linked to the patients initial screening and treatment data.

Further enhancements planned for the no-cost extension year include: Continued development of the outcomes survey process. The development of tools to evaluate and correct data quality issues such as missing or incorrect subject information, further development of standardized and specialized study reports and formalization of system policies and procedures. Also, it is hoped that with anticipated enhancements to computer systems at the state's first responder agency, that we will also be able to link prehospital information direct from the scene and provide a full life cycle of data from the scene, to treatment, to outcomes.

Provide staffing and facilities to monitor patients and collect designated specimens

Sub-project 1: Vital Signs (VS) Data in Trauma Patients

Pre-hospital Vital Signs Data Collection (VSDC) system

During Year 1 emphasis was placed on the development of equipment and working with pre-hospital providers to expand capabilities to obtain pre-hospital vital signs data.

Year 2 focused on further developed the pre-hospital VS analysis to allow auto cleaning of VS artifacts. Critical episodes of hypoxia (SpO2 <95%, <90% <75%, hypotension (SBP<90; <100 mmHg) and tachycardia (HR>120, >110,>100 bpm) were identified. Available pre-hospital cases were linked with trauma registry data for identification of outcomes such mortality, hospital /ICU length of stay, admit and discharge GCS, brain injury status (AIS-head), ISS, etc. In addition, review of medical records was completed to identify pre-hospital LSI (life saving interventions) and during the in-hospital first 4 hour emergency LSI.

During Year 3 a new LifePack system was introduced, and efforts focused on continued retrieval of this data and matching to potential subjects. Analysis was initiated based on vital sign waveform data collected in the pre-hospital management and during the first 60 minutes after admission to identify trends and prediction value of waveforms as compared to need for lifesaving interventions (LSIs) and outcomes

In-hospital Vital Signs Data Collection (VSDC) system and Shock Trauma Physiological (STP) Registry has been upgraded

A limited system for vital signs data collection was in existence prior to the reassignment of

this sub-project to the larger study, emphasis in Year 1 was on system upgrades and expansion of VSDC capabilities. Expansion of the VSDC system from initial location in the Trauma Resuscitation Unit (12 admission bays and 6 operating bays) to a total of 54 critical care bays/beds occurred during Year 1. Data mining was initiated and preliminary algorithms developed.

During Year 2 the VSDC system was further developed. Due to the low return on consents able to be obtained for subject participation, an amendment for a waiver of consent was submitted and approved by both UMB and USAMRMC.

In Year 3, based on the gap analysis, our research findings demonstrate the following:

1) For the methods of predicting patient outcomes (mortality, length of stay and 3,6,12 month GOSE), the dose of patient VS above or below the critical limit (SBP<90, ICP>30, CPP<50 etc) is a better predictor than the signal value alarm.
2) It is difficult to quickly identify the patterns of multi-VS critical episodes at a glance for the duration of 12/24 hours.
3) For real-time ICU management it is important to show a quick overview of the patient in the unit (12 bays). To address the above challenges we developed a real-time ICU Team View (ICUTV) which providing at-a-glance views of the 12 bed ICU VS trends and critical episode. The ICUTV was deployed at the shock trauma center neuro trauma ICU (12 Bays) with a secured remote physician office access.

During Year 3, development of computer assisted auto patient physiological (VS) data identification software was also completed and introduced. This software facilitated the matching of 99.2% of the trauma admissions and ultimate enrollment of 4,995 study subjects meeting enrollment criteria. With improvements in the ability to accurately identify study subjects, a protocol modification is planned for the first quarter of Year 4 (no-cost extension year) to increase the number of data sets available for analysis. Development and refinement of continuous vital signs based prediction models are on-going and preliminary results (see the attached abstracts) have been presented during the course of Year 3.

Sub-project 2: Early Support of Intracranial Perfusion – Cytokines

Much of Year 1 focused on the standardization of policies and procedures for recruitment, specimen and data collection. The sub-project coordinator was assigned and identified research staff trained on recruitment and specimen/data collection procedures. Screening for this sub-project was opened on 8/20/08.

At the close of Year 2, 42 subjects had been enrolled in the study, with one screen-fail and one subject withdrawn. Eight of the 42 subjects expired due to their injuries. Preliminary analysis has focused on the first 30 cytokines subjects to study the relationship between the continuous patient VS (ICP, CPP, SBP, HR Variability and Pause Pressure Variability) and outcome (Mortality, hospital length of stay, surgical management, 3 Month and 6 Month GOSE).

Enrollment of the 50 subject target was completed in Year 3 (January 2010), and follow-up through the first year post injury will be completed on all subjects by January 2011. To date 10 of the 50 subjects have expired due to their injuries. Of those remaining subjects, 38 have completed their 3 month follow-up, 36 have completed their 6 month follow-up, and 26 have completed their 12 month follow-up. One subject declined further follow-up upon contact at 6 months, and two were not able to be reached after multiple attempts. The overall completion rate of follow-ups is 94% at this point.

During Year 3, analysis of serum samples for the first half of the study cohort has been completed and all CSF samples have been analyzed. Data analysis is ongoing with preliminary data presented at the Annual Meetings of the Eastern Association for the Surgery of Trauma, the American Association for the Surgery of Trauma, and the Neurocritical Care Society. Two manuscripts are in process for submission to the Journal of Trauma and Neurocritical Care. Additional data analysis is ongoing.

Sub-project 3: Animal Model of Brain Injury

At the end of Year 3 the Controlled Cortical Impact (CCI) device for use in both the large and small animal models was purchased. The device is scheduled to arrive at UMSOM by the end of October, 2010. Experiments using this device with both rats and pigs will begin as soon as it arrives. Dr. Kwaku Thompson, a new NIH Trauma T32 Research Fellow will be assigned to this project.

Sub-projects: Retrospective

During Year 3, electronic data retrieval and analysis for these 2 sub-projects was completed.

TBI and Fracture Fixation: The records for 167 consecutive TBI patients with femoral shaft fractures between 06/2002 and 06/2009 were reviewed. Patients with a head AIS >2 who survived at least 12 hours beyond admission were included in analysis. Preliminary analysis yielded, one abstract that was presented in June of 2010 at the National Neurotrauma Symposium (see abstract attached)

TBI, Oxygenation and Outcomes: The records of 1660 consecutive patients with TBI admitted between 6/2002 and 6/2009 were reviewed. Patients with a head AIS $\geq$ 3 who survived at least 12 hours beyond admission were ultimately included in the study. Preliminary analysis is near completion and an abstract is under-development for submission in early October 2010.

Implement laboratory evaluation of inflammatory cytokines
Provide staffing, equipment, facilities and training to process study cytokine specimens

Sub-project 2: Early Support of Intracranial Perfusion – Cytokines

Standardization of procedures for handling of specimens collected and specimen storage was completed during the fourth quarter of Year 1. A technician was assigned to assist with specimen processing.

At the close of Year 2 sufficient assay materials required for processing the first 30 study subjects were ordered.

During Year 3, remaining assay materials were acquired and initial processing was completed on CSF samples of all 50 subjects. Serum processing is ongoing. Additional kits are available should repeat testing of any samples be deemed necessary.

Develop an animal model of brain injury
Coordinate with MRMC research institutions to develop this model

Sub-project 3: Animal Models of Brain Injury

The animal use protocol described in the initial statement of work was approved by the UMB IACUC on 9/21/07. It was subsequently submitted to the USAMRMC Animal Care and Use Review Office (ACURO) on 11/27/07. In response to the review by the USAMRMC ACURO, a revised protocol was submitted on 2/25/08 and approved by USAMRMC ACURO on 2/26/08.

During the course of year 2, the model was changed to a large and small animal polytrauma model of contusional brain injury (controlled cortical impact) plus hemorrhagic shock. This change was necessary due to challenges in finding a vendor for the device necessary for conducting the penetrating brain injury paradigm with large animals, and feedback from the review of the last annual report that a large animal model of polytrauma caused by TBI plus hemorrhagic shock would be more clinically translational than that of a rodent model. A revised SOW was developed using a combination of both controlled cortical impact plus hemorrhagic shock with adult male Sprague Dawley rats and with adult male Hanford miniature swine (Sinclair Bio-resources).

In Year 3, the pig CCI model was finalized and approvals received by both UMSOM and ACURO. Development, equipment procurement and initiation of the two planned small and large animal model protocols proved more challenging than originally identified. Over Year 3 the original goal of developing a rat polytrauma model consisting of controlled cortical impact (CCI)-induced contusional brain injury plus hemorrhagic shock was reached. As expected the combination of hemorrhagic shock plus CCI results in death to cells in the cerebral cortex (cortical lesion volume) that is significantly greater than that obtained with CCI alone. One consequence of hemorrhagic shock is a systemic inflammatory reaction that can result in multiple organ failure. While the degree of hypotension induced in our model is not sufficient to produce multiple organ failure, it is sufficient to induce systemic inflammation. We hypothesize that this reaction is responsible for the greater cortical lesion volume observed with the polytrauma model compared to that with CCI alone. Work over the no-cost extension year will test this hypothesis through a series of directed experiments. During the no-cost extension, we will also establish a dose-response relationship between CCI impact depth and cortical lesion volume, using a large animal model consisting of mini-pigs. Progress on this aim has been delayed by the difficulty in finding a company that would supply an appropriate CCI device and stereotaxic head-holder for pigs. The device was ordered late in Year 3 and will be received by the end of October, 2010.

KEY RESEARCH ACCOMPLISHMENTS

Sub-project 1: Vital Signs Data in Trauma Patients

At the close of Year 1

- Enhanced the pre-flight patient Vital Signs data collection network
- Developed and expanded the in-trauma center VS data collection network to cover all critical care bays (TRU, OR, ICU)
- Developed and deployed a total pre and in-hospital VS data collection network
- Developed a basic VS data mining system to collect, process, and predict patient outcomes
- Established a road map for innovative prediction algorithm development

At the close of Year 2

- Completed the hospital/center based real-time patient physiological data collection network (covers all 90 trauma center beds)
- Developed a basic Real time Shock Trauma Physiological (STP) Registry.

Key research findings include:

- Continuous Pre-Hospital VS reviewed by 3 Subject Matter Experts (SME) identified more critical episodes (up to 300%) than Trauma Registry (TR).N=177
- SME identified critical episodes (HR>120 bpm, SpO2<90, SBP<90mmHg) predicted outcome (Mortality, LOS, d/c GCS) better than TR. N=177.
- Continuous Pre-Hospital VS better predicted emergency life saving interventions (LSI) than TR (N=177)
- EMS Pre-Hospital Protocols may be monitored remotely in pre hospital care of Traumatic Brain Injury (TBI). (N=64)

At the close of Year 3

- Development of a computer assisted auto patient physiological (VS) data identification software, facilitating the successful matching of the 2008-2009 STC admission vital signs data for patients fitting enrollment criteria
- Continued development and refinement of continuous vital signs based prediction models
- Development of real-time ICU Team View (ICUTV), providing at-a-glance views of the 12 bed Neuro ICU VS trends

At the close of Year 3, a transition plan for the VS project was initiated. Information on the methods and strategies proposed to move the Vital Signs product to the next phase of development includes submission of a funding request to USAF to examine the Pulse Oximeter signal in more detail than is currently possible with infrastructure and equipment available under the current funding. In brief, the project seeks to identify, test and validate accuracy of algorithms, models and sensors to predict adverse events and the necessity for actionable therapeutic interventions including: hypoxemia, hemorrhagic shock, need for blood transfusion, chest tube insertion, airway management and other life-saving interventions (LSI's), and abdominal surgery to control hemorrhage. The project, titled "Continuous non-invasive monitoring and the development of predictive triage indices for outcome following trauma," has been submitted and we are anticipating a funding decision in the first quarter of Year 4.

Sub-project 2: Early Support of Intracranial Perfusion – Cytokines

At the close of Year 2

- Recruitment of 42 study subjects

30 cytokines cases were used to study the relationship between the continuous patient VS (ICP, CPP, SBP, HR Variability and Pause Pressure Variability) and outcome TBI patient outcome (Mortality, hospital length of stay, time of craniotomy, 3 Month, 6 Month and 12 month GOSE). The findings are

- ICU ICP>20, 30 CPP<50<60 predicts patient outcome better than patient charts VS.
- Combined ICP>20 and CPP<60 episodes predict outcome better than individual ICP and CPP.
- Pressure-time dose of automated ICP and CPP data predicts outcomes in severe TBI.
- The "Brain Trauma Index": Dynamic 3-D Scoring in the Assessment of TBI
- Computerized patient vital signs charting method enhances real-time record keeping in ICU
- Heart Rate Variability Is Associated With Intractable Intracranial Hypertension And Cerebral Hypoperfusion

At the close of Year 3

- Recruitment of targeted 50 subjects
- Preliminary processing of serum and CSF samples for all subjects
- Analysis of all samples and correlation to clinical markers of TBI severity
- Determination of serum and SCF biomarkers that predict worsening of cerebral hypoperfusion, intracranial hypertension, and cerebral hypoxia.

Sub-projects – Retrospective

TBI and Fracture Fixation

At the close of year 3, preliminary analysis completed, key findings include:

- Early femur fracture fixation in TBI subjects correlates with significantly reduced hospital and ICU length of stay
- Early definitive fracture stabilization has no detrimental effect on mortality and discharge GCS

TBI, Oxygenation and Outcomes

At the close of year 3, preliminary analysis nearing completion, early key findings include:

- Hyperoxemia within the first 24 hours of hospitalization increases mortality and worsens short-term functional outcomes in TBI subjects.
- Poor outcomes may be predicted by hypoxia within the first 24 hours of admission

Sub-project 3: Animal Model of Brain Injury

At the close of Year 2

- A rat polytrauma model consisting of controlled cortical impact traumatic brain injury plus hemorrhagic shock has been successfully developed.
- Preliminary experiments performed with human cerebrospinal fluid samples indicate that

they can be used in a new and novel assay that detects toxicity of these samples on culture cell lines, using cellular respiration and glycolysis as outcome measures

REPORTABLE OUTCOMES

a) Presentations:

American Association for the Surgery of Trauma (AAST 2010) Annual Meeting, September 2010

Relationship of serum biomarkers to depth and duration of secondary insults following severe TBI.
Stein D, Lindell A, Murdock K, Menaker J, Keledjian K, Bochicchio G, Scalea T.

Dynamic three-dimensional scoring of cerebral perfusion pressure and intracranial pressure provides a Brain Trauma Index that predicts outcome in patients with severe TBI.
Kharaman S, Dutton R, Hu P, Stansbury L, Hess J, Xiao Y, Stein D, Scalea T.

8th Annual Neurocritical Care Society Meeting, September 2010

Association of CSF biomarkers and secondary insults following severe traumatic brain injury. Stein D, Kufera J, Lindell A, Murdock KR, Menaker J, Bochicchio GV, Aarabi B, Scalea TM.

Depth and duration of secondary insults predicts outcome in patients with severe traumatic brain injury. Stein D, Hu P, Kahraman S, Brenner M, Sheth K, Aarabi B, Scalea TM

NNS 2010: 28th Annual National Neurotrauma Symposium, June 2010

Early hypotension redefined in patients with severe TBI. Stein, DN, Brenner M, Sheth K, Hu P, Aarabi B, Scalea T.

Early fracture fixation improves select outcomes in TBI patients.
Brenner M, Stein DM, Hu P, Scalea T

Association of University Anesthesiologists, Annual Meeting, Denver Colorado, May 2010

New uses of vital signs signals during resuscitation to triage, assess provider performance and predict outcomes.
Mackenzie CF, Hu PF, Ayan S, Woodford M, Floccare D, Scalea T.

2010 American Telemedicine Association Annual International Meeting May 16-18, 2010 San Antonio, TX

High frequency ICU perfusion pressure critical episodes predicts TBI patient outcomes. Hu P, Akozer S, Dutton R, Stein D, Murdock K, Xiao Y, Scalea T.

International Society for Magnetic Resonance in Medicine, May 1-7, 2010, Stockholm, Sweden

Early diffusion changes following controlled cortical impact injury on a rat model. Zhuo J, Xu S, Racz J, Fiskum G, Gullapalli R.

Early metabolic changes following focal traumatic brain injury in rats measured using 1H MRS. Xu S, Roys S, Racz J, Shi D, Zhou J, Gullapalli R, Fiskum G.

6th Innovations in the Surgical Environment Conference March 25-27 2010 Annapolis, MD.

Trauma center wide real-time patient vital signs data registry (VSDR) for improvement of patient safety. Hu P, Stein D, Xiao Y, Dutton R, Kahraman S, Yeatts D, Grissom T, Mackenzie C, Scalea T.

Eastern Association for the Surgery of Trauma (EAST) 23rd Annual Scientific Assembly, Phoenix, AZ. January 2010

CSF levels of NSE and S100B in patients with severe TBI: correlation with clinical measures. Stein DM, Murdock KR, Kufera JA, Menaker J, Bochicchio GV, Dutton RP, Aarabi B, Scalea TM.

SCCM's 39th Critical Care Congress January 9-13, 2010 in Miami Beach, Florida, USA.

Heart rate variation is associated with intractable intracranial hypertension and cerebral hypoperfusion.
Kahraman S, Dutton R, Hu P, Stansbury L, Xiao Y, Stein D, Scalea T .

Critical care monitoring in the field: Pre-hospital continuous vital signs acquisition identifies best predictors of life-saving interventions in trauma patients. Sen A, Hu P, Mackenzie C, Dutton R, Jordan S, Xiao Y, Scalea T.

Cerebrospinal fluid levels of inflammatory mediators: association with outcome following severe traumatic brain injury. Stein DM, Murdock KR, Menaker J, Bochicchio GV, Dutton RP, Aarabi B, Scalea TM.

American Medical Informatics Association AMIA 2009 Annual Meeting (Nov 14-18, 2009) San Francisco, CA

CPP/ICP dose index: Dynamic 3-D scoring in the assessment of TBI. Kahraman S, Hu P, Xiao Y, Dutton R, Stein D, Scalea T.

Computerized patient vital signs charting method enhances real-time record keeping in ICU. Hu P, Akozer S, Lindell A, Liu K, Mitrou M, Gettings L, Stein D, Xiao Y.

Is there added value in continuous vital signs and video collection linked to trauma patient outcomes? Hu P, Mackenzie CF, Xiao Y, Seebode D, Wong M, Murdock K, Dutton R.

American Society of Anesthesiologists ASA2009 Annual Meeting (October 17-21, 2009) New Orleans, LA

Real-time patient vital signs data registry for trauma patient care. Dutton R, Hu P, Xiao Y, Yeatts D, Mackenzie C.

High resolution ICP and CPP data better predict outcome of severe TBI. Dutton R, Kahraman S, Hu P, Xiao Y, Scalea T.

American Association for the Surgery of Trauma AAST 2009 Annual Meeting (October 1-3, 2009) Pittsburgh, PA

Pressure-time dose of automated ICP and CPP data predicts outcomes in severe TBI. Kahraman S, Hu P, Xiao Y, Dutton R, Aarabi B, Stein D, Scalea T.

16th World Congress of Disaster and Emergency Medicine (May 12-16 2009) Victoria, BC, Canada

Continuous vital signs acquisition improves prehospital trauma triage. Sen A, Hu P, Mackenzie C, Jordan S, Xiao Y, Dutton R, Scalea T

In-flight vital signs blackbox for trauma care. Hu P, Mackenzie C, Dutton R, Sen Y, Xiao Y, Floccare D, Scalea T.

Video technologies in emergency health research in assessing quality of care: a study of trauma resuscitation milestones. Sen A, Hu P, Mackenzie C, Xiao Y, Dutton R.

American Telemedicine Association Conference, (April 26-29, 2009) Las Vegas, NV

Automated vital-sign recording identifies more critical episodes than chart abstraction. Hu P, Sen Y, Mackenzie C, Xiao Y, Jordan S, Dutton R, Scalea T, and Trauma Vital Signs Research Group (TVSG)

Can EMS protocols be monitored remotely in pre hospital care of traumatic brain injury (TBI)? Mackenzie C, Hu P, Sen A, Xiao Y, Jordan S, Dutton R, Scalea T.

Presented at the American Medical Informatics Association Annual Symposium (November 8-12, 2008) Washington DC

Automatic pre-Hospital vital signs waveform and trend data capture fills quality management, triage and outcome prediction gaps. Mackenzie C, Hu P, Sen A, Dutton R, Seebode S, Floccare D, Scalea T.

Statewide real-time in-flight trauma patient vital signs collection system. Hu P, Mackenzie C, Dutton R, Sen A, Xiao Y, Handley C, Ho D, Scalea T.

American Society of Anesthesiologists Annual Conference (October 18-22, 2008) Orlando, FL.
Continuous prehospital vital signs record identifies increased abnormalities/predicts interventions. Sen A, Hu P, Mackenzie C, Jordan S, Dutton R.

American Telemedicine Association Annual meeting (April 6-9, 2008) Seattle, WA.
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CONCLUSIONS

At the conclusion of Year 3 significant progress has been made toward meeting overall project milestones. The infrastructure of staff, technology and data management to support the completion of sub-projects and long-term assessment of TBI patients had been created. The robust Brain Resuscitation Registry (BRR) needed to accomplish the goals of this multi-year project has been implemented and continues to undergo refinement. Recruitment and data collection for the Vital Signs human sub-projects is ongoing, and well as data analysis and prediction model development. Sub-project 2, Cytokines has completed recruitment, preliminary specimen processing is completed, data analysis has been initiated and final subject follow-ups will be finished in January 2011. Revisions to the animal sub-projects are complete, needed materials have been purchased and research activities will occupy the no-cost extension year. Two retrospective human sub-projects are nearing completion of data analysis. The protocol for the final new human use sub-project will be submitted for approvals in October 2010

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No new literature searches were undertaken in Year 3.

In preparation for the new human use protocol, TCD and BAM the following article was located to serve as a foundational resource and an expanded literature search is planned for the future

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APPENDICES

Abstracts Accepted or Presented since last Annual Report

Relationship of Serum Biomarkers to Depth and Duration of Secondary Insults Following Severe TBI

Background: Neuroinflammation is a predominant feature of severe traumatic brain injury (sTBI). The management of sTBI focuses on prevention and treatment of intracranial hypertension (ICH) and cerebral hypoperfusion (CH). This study investigated the systemic effects of neuroinflammation and its relationship to clinical measures of disease severity.

Methods: Patients with head AIS>3, age>14, "isolated" TBI, need for intracranial pressure (ICP) monitor, and deemed survivable were prospectively enrolled. Serum and CSF were collected within 24 hours of injury and twice daily for 7 days. Specimens were analyzed by multiplex bead array assays. Pressure times time (PTD) was calculated for 12-hour periods for depth and duration of episodes of ICH (ICP>20mmHg) and CH (cerebral perfusion pressure; CPP<60mmHg). Outcome was measured by Extended Glasgow Outcome Scale (GOSE) at 6 months.

Results: 25 patients were enrolled. Matched CSF was available in 11. Mean head AIS was 4.2±0.7, Marshall score was 2.6±0.7, and admission GCS was 6.3±4.0. Elevated serum and CSF levels of IL-1ß, IL-6, IL-8, IL-10 and TNF-□ were found in all patients. Correlations were found between serum levels of IL-8 and TNF-□ and PTD of ICH ($r=0.44$ and $r=0.43$, $p<0.05$) and CH ($r=0.54$ and $r=0.25$, $p<0.05$). No correlations between CSF levels and clinical variables were noted. Mean admission and bi-daily levels of IL-8 were higher in patients with poor outcome (GOSE <5).

Conclusions: Inflammatory mediators are detectable in the serum of patients with sTBI. Elevated levels of IL-8 and TNF-□ in the serum, but not CSF, during episodes of ICH and CH imply there are significant systemic effects of these events. These serum biomarkers are promising as diagnostic or therapeutic targets and have significant implications for the role of inflammatory system manipulation in the management of sTBI.

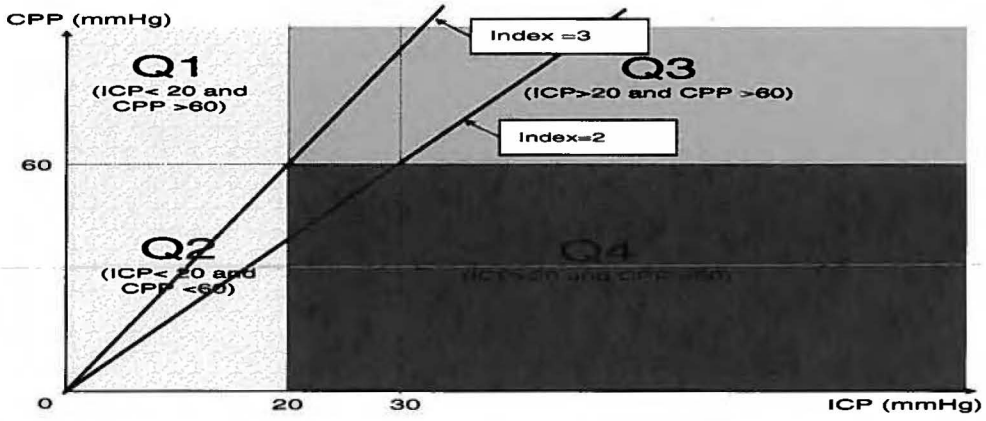
Mean Daily Values (pg/ml)			
	Good Outcome n=15	Poor Outcome n=9	*p value*
IL-1b	49.3 ±170.8	6.5 ±15.7	*0.01*
IL-6	108.1 ±172.9	251.6 ±1338.6	*0.17*
IL-8	24.4 ±20.1	95.7 ±383.3	*0.02*
IL-10	66.7 ±163.5	52.7 ±66.4	*0.40*
TNF-a	8.0 ±4.2	11.7 ±13.5	*<0.001*
Peak Admission Values (pg/ml)			
	Good Outcome n=15	Poor Outcome n=9	*p value*
IL-1b	65.6 ±246.5	8.8 ±11.4	*0.53*
IL-6	174.6 ±146.4	144.2 ±151.0	*0.63*
IL-8	31.5 ±19.1	67.4 ±57.0	*0.03*
IL-10	106.5 ±287.4	48.8 ±56.3	*0.56*
TNF-a	8.03 ±7.7	9.2 ±4.5	*0.69*

Dynamic Three-Dimensional Scoring of Cerebral Perfusion Pressure and Intracranial Pressure Provides a Brain Trauma Index that Predicts Outcome in patients with Severe TBI

Background: Data on intracranial and cerebral perfusion pressure (ICP, CPP) guide therapy in severe traumatic brain injury (TBI), but current linear analytic methods are insufficiently sensitive and specific for prognosis in dynamic situations over time.
Methods: We have developed algorithms incorporating continuous, automated, digital ICP and CPP monitoring data into a pressure-times-time 'dose' (PTD) function. In the present study, we calculated cumulative doses using thresholds of ICP>20 mmHg and CPP <60 mmHg and graphed these as a Brain Trauma Index (BTI). We then compared the predictive power of BTI <3 and <2 for 30-day mortality, 3- and/or 6-month Extended Glasgow Outcome Scale (GOSE) <5, using receiver operator characteristics (ROC) analysis. We then graphed BTI values for each patient as linear functions over time as a step toward development of a real-time bedside monitoring tool.
Results: Twenty eight subjects yielded 2858.4 hrs of data (1,715,040 data points). BTI<3 and <2 were better than ICP>20 mmHg in predicting mortality (p=0.001). BTI<2 was more powerful than CPP<60 mmHg in predicting unfavorable GOSE at 3and 6 months (p<0.05).

Conclusion: Calculation of a BTI from continuous digital data predicts outcome in severe TBI and has potential for the design of real-time bedside early-warning systems

Figure 1: Slopes defining critical quadrants of Brain Trauma Index.



Association of CSF Biomarkers and Secondary Insults Following Severe Traumatic Brain Injury

Background: Management of severe traumatic brain injury (TBI) focuses on mitigating secondary insults. There are a number of biomarkers that are thought to play a part in secondary injury following severe TBI. Two of these, S100ß and neuron-specific enolase (NSE), have been extensively studied in the setting of neurological injury. This pilot study was undertaken to investigate the relationship of S100ß and NSE to clinical markers of severity and poor outcome: intracranial hypertension (ICH) and cerebral hypoperfusion (CH).

Methods: Patients at the R Adams Cowley Shock Trauma Center were prospectively enrolled over an 18-month period. Inclusion criteria were: age >18, admission within the first 6 hours after injury, Glasgow Coma Scale (GCS) <9 on admission, isolated TBI, and placement of an intraventricular catheter (IVC). Patients were managed according to an institutional protocol based on the Brain Trauma Foundation Guidelines. CSF was collected from the IVC on admission and twice daily for 7 days. S100β and NSE levels were analyzed by ELISA. CSF levels drawn before (PRE) and after (POST) 12-hour time periods were compared to percentage time intracranial pressure (ICP) >20 mmHg (% ICP_{20}) and cerebral perfusion pressure (CPP) <60 mmHg (% CPP_{60}), and cumulative 'Pressure times Time Dose' (PTD) for episodes of ICP >20 mmHg (PTD ICP_{20}) and CPP <60 mmHg (PTD CPP_{60}). Statistical analysis was performed using the Student's *t* test and non-parametric Wilcoxon statistic to compare means based on continuous data. Linear regression methods were applied to compare levels of S100β and NSE with ICP and CPP.

Results: Twenty-three patients were enrolled. The cohort of patients was severely injured and neurologically compromised on admission (admission GCS = 5.6 ±3.1, Injury Severity Score [ISS] = 31.9 ±10.6, head Abbreviated Injury Scale [AIS] = 4.4 ±0.7, Marshall score = 2.6 ±0.9). Elevated levels of S100β and NSE were found in all 223 CSF samples analyzed. ICH was found to be associated with PRE and POST S100β levels when measured as % ICP_{20} ($r=0.20$ and $r=0.23$, $p<0.01$) and PTD ICP_{20} ($r=0.35$ and $r=0.26$, $p<0.001$). POST increasing NSE levels were weakly correlated with increasing PTD ICP_{20} ($r=0.16$, $p=0.01$). PRE S100β levels were associated with episodes of CH as measured by % CPP_{60} ($r=0.20$, $p=0.002$) and both PRE and POST S100β levels were associated with PTD CPP_{60} ($r=0.24$ and $r=0.23$, $p<0.001$). PRE and POST NSE levels were also associated with episodes of CH as measured by % CPP_{60} ($r=0.22$ and $r=0.18$, $p<0.01$) and PTD CPP_{60} ($r=0.20$ and $r=0.21$, $p<0.01$).

Conclusions: In this preliminary analysis, S100β levels were associated with ICH and CH over a full week of ICP monitoring. We also found associations between CH and NSE levels in CSF of patients with severe TBI. Our results suggest that there is an association between levels of ICH and CH and these biomarkers when measured prior to episodes of clinically significant secondary insults. These markers of neuronal cell death demonstrate promise as both indicators of impending clinical deterioration and targets of future therapeutic interventions.

Depth and Duration of Secondary Insults Predicts Outcome in Patients with Severe Traumatic Brain Injury

Introduction: Secondary insults following severe traumatic brain injury (sTBI) are known to be associated with poor outcome. Automated continuously recorded vital signs have been shown to be superior to manual recordings in capturing these events. The purpose of this study was to investigate the use of automated continuously recorded vital signs early after injury to predict outcome following sTBI.

Methods: Patients with head AIS≥3, age>14, "isolated" TBI and need for intracranial pressure (ICP) monitoring were prospectively enrolled. Outcome was measured by Extended Glasgow Outcome Scale (GOSE) at 6 months. Continuous, automated, digital data was collected every 6 seconds. Five minute means were calculated and mean values over the duration of monitoring were recorded. Percent time (% time) and pressure time dose (PTD, mmHg*h) above and below thresholds (ICP>20 and >30 and CPP<50 and <60) were calculated and analyzed to compare their ability to predict 30-day mortality and functional outcome by ROC.

Results: 60 patients were enrolled. Demographics included: mean age 34 years (range 16-83), mean admission GCS of 6.4 ±3.1, mean head AIS of 4.2 ±0.7 and mean Marshall score of 2.5 ±0.9. The 30-day mortality rate was 13%. 35 patients had good neurological outcomes (GOSE>4). Moderate (CPP<60) and severe (CPP<50) cerebral hypoperfusion and moderate (ICP>20) and severe (ICP>30) intracranial hypertension as measured by %time or PTD were predictive of both mortality (AUC range 0.85-0.75, $p<0.05$) and poor neurological outcome (0.68-0.78, $p<0.05$). PTD of cerebral hypoperfusion better predicted poor functional outcome

Conclusions: Automated continuously recorded vital signs early after injury are useful in predicting outcomes in patients with sTBI. Cerebral hypoperfusion and intracranial hypertension are clearly associated with poor outcome. Automated processing of measures that account for both depth and duration of secondary insults shows promise in the development of predictive models for patients requiring intervention and has potential for the design of real-time bedside early-warning systems.

Early Hypotension Redefined in Patients with Severe TBI

Purpose of the study: Secondary insults following severe traumatic brain injury (sTBI) are known to be associated with poor outcome. Automated continuously recorded vital signs have been shown to be superior to manual recordings in capturing these events. The purpose of this study was to investigate the use of automated continuously recorded vital signs early after injury to predict functional outcome following sTBI.

Methods: 28 patients with head AIS≥3, age>14, "isolated" TBI and need for intracranial pressure (ICP) monitoring were prospectively enrolled at a single large urban tertiary care facility. Outcome was measured by Extended Glasgow Outcome Scale (GOSE) at 3 months. Continuous, automated, digital data was collected every 6 seconds for 72 hours after admission. Five minute means were calculated and minimum, maximum, and mean values over the 1st 12, 24, 48, and 72 hours of ICU admission were captured for systolic blood pressure (SBP), mean arterial blood pressure (MAP), heart rate (HR), ICP, cerebral perfusion pressure (CPP), and oxygen saturation (Sp02). Percent time (% time) and pressure time dose (PTD) above and below thresholds (SBP<90, <100, <110 and <120, MAP<60 and <70, HR>100 and >120, ICP>20 and >30, CPP<50, <60, and >100, SpO2 <88 and <92) were calculated for these time periods and analyzed to compare their ability to predict GOSE by ROC analysis **and calculation of sensitivity and specificity.**

Summary of results: Demographics included: mean age 35.5 years (range 17-65), mean admission GCS of 5.0 ±1.9, mean head AIS of 4.1 ±0.7 and mean Marshall score of 2.4 ±1.0. The 30-day mortality rate was 14%. 11 patients had good neurological outcomes (GOSE >4). Traditional markers of poor outcome (age, admission GCS, Marshall score, head AIS) were no different between the groups with good and poor outcome. Moderate (CPP<60) and severe (CPP<50) cerebral hypoperfusion were predictive of poor neurological outcome for all 4 time periods (AUC range 0.87-0.68, $p<0.05$). Intracranial hypertension (ICP>20) was predictive of poor outcome for 24, 48, and 72 hour periods of ICU monitoring (AUC range 0.75-0.69, $p<0.05$). Within the 1st 12 hours of ICU admission, SBP was also found to be predictive of poor outcome. PTD SBP <110, PTD and % time SBP <100, and minimum SBP were highly correlated with poor outcome. There was a trend toward poor outcome in patients with SBP <120 in the 1st 12 hours of ICU admission as well (Figure).

Conclusions: Automated continuously recorded vital signs early after injury are useful in predicting functional outcome in patients with sTBI. Cerebral hypoperfusion, intracranial hypertension and systemic hypotension are clearly associated with poor outcome. Traditional definitions of hypotension, namely SBP <90, may underestimate the effect of systemic hypoperfusion on neurological recovery. Systemic blood pressure targets closer to 120 may be more efficacious in minimizing secondary insults. More work is needed to validate these preliminary findings.

Early Fracture Fixation Improves Select Outcomes in Traumatic Brain Injury Patients

Introduction: There are several conflicting studies investigating the correlation between early definitive femur fracture fixation and outcomes in traumatic brain injury (TBI) patients. Our goal was to determine if timing of fracture fixation could predict patient outcomes.
Methods: We retrospectively reviewed 167 consecutive TBI patients with femoral shaft fractures between 06/2002 and 06/2009 at a large urban tertiary care facility. All patients with a head AIS>2 who survived at least 12 hours beyond admission were included in the study. Patients were grouped according to timing of definitive femur fracture fixation. Outcomes variables included mortality, intensive care unit (ICU) and hospital length of stay, and discharge Glasgow Coma Scale (GCS). Logistic regression analysis was used to determine whether early (<24 hours) or late (>24 hours) fracture fixation correlated with patient outcomes.
Results: The majority of patients (n= 121 or 72.5%) were male and admitted for blunt trauma (n= 165 or 99%). Mean age, admission GCS, and ISS scores were 32 ± 16 years, 11.1±4.7, and 33±12. ICU and hospital length of stay was 8.1±10.7 and 14.3±11.9 days. Average discharge GCS was 13.1+ 3.1 and the mortality rate was 5 %. One-hundred and sixty-five patients were treated with intra-medullary nailing, and two patients received external fixation devices as definitive treatment. A total of 50 patients underwent early definitive fracture fixation within twenty-four hours, while the remaining 117 patients underwent a later operation. After controlling for age, gender, Injury Severity Score, mechanism of injury, and admission GCS, patients who underwent definitive femur fracture fixation within 24 hours of admission had significantly shorter ICU length of stay (p=0.001, OR 0.19, CI 0.07-0.51) and hospital length of stay (p<0.0001, OR 0.08, CI 0.03-0.18) than those patients whose operation occurred later. Discharge GCS and mortality were not found to correlate with timing of fracture fixation in the first 24 hours of hospitalization.
Conclusion: Early femur fracture fixation in TBI patients correlates with significantly reduced hospital and ICU lengths of stay. Furthermore, early definitive fracture stabilization has no detrimental effect on mortality and discharge GCS as previous studies have reported.

New Uses of Vital Signs Signals During Resuscitation to Triage, Assess Provider Performance and Predict Outcomes

Introduction: Increasing patient survivability by predicting outcomes, anticipating life saving interventions (LSI) and making accurate triage decisions are major objectives of resuscitation. A critical decision is made every 72 seconds during initial management (1) and protocol compliance occurs in only 53% of trauma patient resuscitations when measured prospectively (2). Vital signs (VS) data collected in pre-hospital care, during initial trauma center resuscitation and recorded in the trauma registry (TR) are often missing or unreliable (3). We used a device to automatically and continuously collected pre-hospital data to test the hypothesis that VS predict need for trauma center care, LSI and provider performance better than use of retrospectively compiled TR data or other triage tools.

Methods: After IRB approval, 6 helicopters in Maryland Emergency Medical Services were equipped with a Vital Signs Data Recorder (VSDR) to capture continuous VS from patients. Pre-hospital LSI (fluid bolus, chest decompress, intubation, CPR etc) and those LSI carried out within 2 hours after arrival in the trauma center were considered outcome variables. VSDR and TR data were reviewed by three experts and findings compared using Bland- Altman method when the intra-class correlation coefficient (ICC) between three subject raters was high. A multivariate analysis was performed to determine which VS variable best predicted LSI's using the values in the TR and the VSDR and t-tests to compare prediction of VSDR data with other triage tools (TRISS, RTS).

Results: Pre-hospital VSDR data were collected in 177 patients. The ICC between three raters ranged from 0.72-0.98. There was significant difference ($p<0.001$) from TR data in highest and lowest heart rate(HR), systolic blood pressure (SBP), oxygen saturation (SpO2). VSDR HR (>120/min) and SpO2 (<90%) predicted LSI, while none of the TR VS did so in a multivariate model (Table 1). The area of receiver-operator-curve (ROC) for the VSDR data was 0.82 in the model which was validated by bootstrapping (Table 2). VSDR and TR data showed that SBP was not an independent predictor of LSI and SBP< 90 did not identify any patient needing a LSI. End-tidal carbon dioxide (ETCO2) assessed provider performance (Fig 1) and VSDR SpO2 predicted mortality (ROC 0.84).

Conclusions: VSDR data increased the odds of predicting LSI's and SpO2 identified patients who died. TRISS would be different with VSDR data that identified BP<90mm Hg in ½ patients missed by TR. The VSDR data triaged need for trauma center care (mortality) better than TR data. ETCO2 identified performance to Brain Trauma Foundation pre-hospital head injury management protocols (4). By increasing the VS accuracy beyond TR and providing continuity of real data, real-time VS acquisition may provide better trauma prognostic models to reduce adverse outcomes and cost associated with current 35-65 % trauma patient triage errors

High Frequency ICU Perfusion Pressure Critical Episodes Predicts TBI Patient Outcomes

Introduction: Continuous monitoring of intracranial pressure (ICP) and cerebral perfusion pressure (CPP) for traumatic brain injury (TBI) patients in intensive care units (ICU) may be performed at bedside and telemedically by specialists. However, most outcome predictors derived from high frequency monitoring are currently based on hourly manual charting. Critical episodes of perfusion pressure (ICP >20 and CPP <60 mm Hg) occur frequently but often go unrecorded by standard chart recording. We report a real-time high frequency ICU ICP and CPP collection and episode calculation method which predicts outcome.

Methods: With IRB approval, we studied 30 severe TBI patients (defined as Glasgow Coma Scale GCS <9, requiring ICP monitoring). Trauma Center wide real-time high frequency ICU patient monitor (GE Marquette) digital recorder were developed for continuous recordings of ICP and CPP at 6 sec time intervals. Potential artifacts were cleaned by a moving median with a window-size of 5 data points (30 sec). Five min mean values and episode of ICP >20, CPP <60 mm Hg were calculated for total ICU stay (4.6 +/- 2.6 days)/ We calculated the prediction values for three unfavorable outcome measures (28-day mortality, discharge GCS<13 and 3-month Extended Glasgow Outcome Scale (GOSE) <5) using receiver operating characteristics (ROC) methods.

Results: The area under the ROC curve of ICP >20, CPP <60 mm Hg thresholds for predicting GOSE were 0.83 and 0.84; for mortality were 0.67 and 0.73 and for discharge GCS were 0.84 and 0.74 respectively. The both critical episodes of ICP >20 and CPP <60 mmHg showed statistically significant prediction value { p=0.001-0.042.}.

Conclusion: High frequency ICU perfusion pressure critical episodes may be used to develop a real-time TBI ICU patient treatment index to provide in-time reminder for the care providers. Future telemedicine systems may benefit from such an index to improve real-time patient care.

Early Diffusion Changes Following Controlled Cortical Impact Injury on a Rat Model

Introduction: The understanding of tissue alterations at an early stage following traumatic brain injury (TBI) is critical for injury management and prevention of more severe secondary damage. Previous studies have shown decreased apparent water diffusion (ADC) within hours after TBI followed by increased diffusion, days or weeks after TBI12. Understanding tissue changes very early following injury can provide an insight into possible treatment windows. In this study, we investigated the early changes in tissue water diffusion following mild to moderate controlled cortical impact injury using a rat model.

Methods: TBI model: Six adult male Sprague-Dawley rats (300-350 gms) were subjected to left parietal controlled cortical impact injury. After being anesthetized initially with 4% isoflurane, the rats were maintained at 2% isoflurane, and the left parietal bone was exposed via a midline incision in a stereotactic frame. A high-speed dental drill was used to perform a left-sided 5 mm craniotomy that was centered 3.5 mm posterior and 4 mm lateral to bregma. A 5 mm round impactor tip was accelerated to 5 m/sec with a vertical deformation depth of 1.0-1.5 mm1.5 mm and impact duration of 50 ms. The bone flap was immediately replaced with dental acrylic and the scalp incision was closed with 3.0 silk. The experimental protocol was approved by the Committee for the Welfare of Laboratory Animals of the University of Maryland.

Imaging: All imaging was performed on a Bruker Biospec 7.0 Tesla 30 cm horizontal bore scanner using Paravision V software. A Bruker surface array coil was used as the receiver and a Bruker 72mm linear-volume coil as the transmitter. T2-weighted (TE/TR = 56.8/5500ms, 4 echo train length, 2 averages) and diffusion weighted images (TE/TR = 50/6000ms, single shot spin echo EPI, 30 directions, 5 b0 images, b = 1000s/mm2, 2 averages) were acquired at before the injury and 2 hour and 4 hour after injury. During the entire imaging time, the animal was under 1-2% isoflurane anesthesia and 1 L/min oxygen administration via a nosecone. Both respiration and heart rate were monitored. DTI Analysis: DTI maps were generated offline using FDT (FMRIB's Diffusion Toolbox, Oxford, UK). Regional measures of ADC and FA were obtained from the hippocampus.

Results: At 2 hour after injury, ADC was significantly reduced and FA increased ($p<0.05$) in the ipsilateral hippocampus. FA was also increased ($p<0.05$) in the ipsilateral thalamus. Although non-significant, a trend for ADC reduction was observed bilaterally in the thalamus and the ipsilateral olfactory region ($p<0.1$). For FA, an increasing trend ($p<0.1$) was also observed for the contralateral hippocampus while a decreasing trend ($p<0.1$) was observed in the olfactory region. At 4 hour after injury, a significant increase in FA ($p<0.05$) was observed in the ipsilateral hippocampus and the thalamus. An increasing trend ($p<0.1$) for FA was observed in the contralateral hippocampus and thalamus. Although changes in DTI metrics remained abnormal from the baseline

Discussion: This studied showed a decreased ADC and increased FA in regions in close proximity to impacted regions (ipsilateral hippocampus and bi-lateral thalamus) immediately following TBI, with the ipsilateral hippocampus most affected, followed by ipsilateral thalamus and contralateral thalamus. Remote regions such as the ipsilateral olfactory area were affected to a lesser degree. At the 4 hour time point a large inter-individual variation was observed with an overall trend towards recovery in the ipsilateral hippocampus while the thalamus was still going through significant worsening stage. Our study indicates a distance effect from the site of injury and suggests a therapeutic window of about 2-3 hours to limit the cascade of events that may lead to secondary injury.

Early Metabolic Changes Following Focal Traumatic Brain Injury in Rats Measured Using 1H MRS

Introduction: Traumatic brain injury (TBI) is characterized by acute physiology changes that may play a significant role in the final outcome resulting from such an injury. Experimental models of TBI provide a useful tool for understanding the very early cerebral metabolic changes induced by the damage. Previous in vivo 1H MRS studies indicated a time evolution of TBI. Schuhmann et al showed that total creatine (tCr), N-acetylaspartate (NAA), glutamate (Glu), and choline (Cho) concentrations significantly decreased during the first 24 hour, and then started to increase at 7 days. At the same time, lactate (Lac) increased and reached its peak at 7 days after TBI. Because the early neuro-metabolic changes may offer valuable information for the clinical neuroprotective treatment, in the present study, we investigate the post-traumatic neuro-metabolic changes at 3-hours and 5-hours after TBI following a focal controlled cortical impact injury in rat, using in vivo 1H MRS at 7 Tesla.

Materials and Methods: TBI Model: Six adult male Sprague-Dawley rats (300-350 gms) were subjected to left parietal controlled cortical impact injury. After being anesthetized initially with 4% isoflurane, the rats were maintained at 2% isoflurane, and the left parietal bone was exposed via a midline incision in a stereotactic frame. A high-speed dental drill was used to perform a left-sided 5 mm craniotomy that was centered 3.5 mm posterior and 4 mm lateral to bregma. A 5 mm round impactor tip was accelerated to 5 m/sec with a vertical deformation depth of either 1.0 or 1.5 mm and impact duration of 50 ms. The bone flap was immediately replaced with dental acrylic and the scalp incision was closed with 3.0 silk. The experimental protocol was approved by the Committee for the Welfare of Laboratory Animals of the University of Maryland. In Vivo 1H MRS. All experiments were performed on a Bruker Biospec 7.0 Tesla 30 cm horizontal bore scanner using Paravision 5.0 software. A Bruker 1H surface coil array was used as the receiver and a Bruker 72 mm linear-volume coil as the transmitter. Proton density-weighted MR images were taken using a 2D rapid acquisition with relaxation enhancement (RARE) sequence (TR/TE=5500/9.5 ms) for anatomic reference. A point-resolved spectroscopy (PRESS) pulse sequence (TR/TE=2500/20 ms) was used for data acquisition from a 3 x 3 x 3 mm3 voxel. The voxel covered immediate pericontusional zone, all layers of the hippocampus, and superior thalamic structures. Data were acquired before injury (baseline), at 3-hours, and at 5-hours after injury in both pericontusional voxel (Fig 1A) and the corresponding contraleteral side (Fig 1B). For each spectrum, 300 acquisitions were averaged for a total of 13 min. At all times during the experiment, the animal was under 1-2% isoflurane anesthesia and 1 L/min oxygen administration. Respiratory monitoring was performed and the animal was maintained at 36-37 oC during the entire experiment.

Proton MRS data was fitted using the LC Model package, and only metabolites with standard deviations (SD) % < 20 were included for further analysis. The in vivo mean metabolite concentrations relative to tCr at each time point were subjected to paired one-tail Student t-test in comparison with the control time point.

Results: The in vivo 1H spectra demonstrate good spectral resolution and sensitivity both at the pericontusional side and the contraleteral side. Among the metabolic ratios of, NAA/tCr, Glu/tCr and Cho/tCr demonstrated significant changes over the five hours following injury. No statistically significant differences were found in glutamine, myo-inositol, and taurine concentrations among the

three time points in either the pericontusional voxel itself or in comparison to the contraleteral side. Significant reduction of 32 % and 33 % NAA was observed in the pericontusional voxel at 3-hours and 5-hours after TBI respectively compared to the baseline. Although the contraleteral voxel also exhibited significant reduction in NAA this reduction was much lower compared to the pericontusional side. No significant differences in NAA were found in the pericontusional side between the 3 and 5 hours. In addition to NAA, our results showed that Glu significantly decreased at 3-hours after TBI in the pericontusional voxel, compared to the baseline (0.922 ± 0.137 vs. 1.155 ± 0.202, $p<0.03$) and the contraleteral side (0.922 ± 0.137 vs. 1.12 ± 0.08, $p<0.04$). As with NAA, we did not observe a significant difference between 3-hours and 5-hours in Glu level in the pericontusional side. Cho in the pericontusional voxel was significantly lower than the contraleteral side (0.166 ± 0.014 vs. 0.179 ± 0.013, $p<0.05$) at 3-hours after TBI. Although, the signal intensities of Lac were undetectable during the baseline, varying levels (0.115 - 2.098) of increased Lac signal intensity was observed in the pericontusional voxel at 3-hours and 5-hours after the injury, but not in the corresponding contraleteral voxel.

Discussion: This study shows that there exists a temporal window of brain vulnerability after TBI in rat, which is in line with previously studies [2]. Furthermore, our investigation demonstrates that the neuro-metabolic changes following TBI associated with NAA, Glu and Cho may have their most significant changes as early as three hours after the injury. Since the pericontusional voxel chosen in this study is of special clinical interest for neuroprotective treatment strategies, our finding may indicate a temporal window of about 3 hours for planning interventions that target cerebral energy metabolism.

Trauma Center Wide Real-time Patient Vital Signs Data Registry (VSDR) for Improvement of Patient Safety

Introduction: Continuous display of patient physiological data is standard patient care practice but real-time recording, retrieval and processing of such data is not. In time-critical, multi-tasking domains requiring life-saving interventions, documentation is sparse. We evaluated reliability of an automated vital signs collection system and tested proof of concept for 24x7 retrospective constructions of events and prospective prediction of patient outcome

Methods: Real-time patient vital signs data feeds from 102 monitors (GE-Marquette-Solar-7000/8000) were networked in a major trauma center to include 12 bed trauma resuscitation unit (TRU), 2 Angio, 1 CT, 6 operating-rooms (OR), 9 post-anesthesia care unit, 36 intensive care (ICU) beds and 36 intermediate care beds. Real-time vital signs waveforms, trends and alarms were compressed and transferred to a centralized VSDR server through the secured hospital intranet and archived. Custom processing and viewing programs (based on MatLab and VisualBasic) were developed for real-time patient data abstraction, artifact removal, 5-60 min time window averaging, Vital Signs (VS) variability and summary data output to both text and MS-Excel format.

The server was interfaced with Trauma Registry which provides over 100 patient-specific demographics and outcomes. Real-time ICU VS viewer was developed to highlight the critical episode of VS and the extend-Dose for past 12 hours, 24 hours and 7 days. In addition a 2-Dimensional display of Shock Index (SBP vs HR) and Brain Trauma Index (CPP vs ICP) were developed to track the ICU patient trajectory in real-time. VS specific processing and prediction software were also developed to allow retrospective construction of events and prospective prediction of patient outcome.

Results: During 18 months over 80 VS variables were collected including continuous electrocardiogram, oxygen saturation, end-tidal carbon dioxide (ECG/SpO2/CO2/Respiration) waveforms at 240Hz. The numerical values of heart rate, blood pressure, intracranial pressure, cerebral perfusion pressure, respiratory rate, temperature, (HR/BP/SpO2/ETCO2/ICP/CPP/RR/TEMP etc) were recorded at every 6 seconds for all 102 patient beds. Raw data was compressed over 90% before being sent to the VSDR server. Data rates after compression averaged 76.4 KB/h for numerical and 12.3MB/h for waveforms. Over 55,000 days (102 patient-locations*365days*1.5 years= 55,845 days) of over 10,000 patients vital signs were collected with system uptime > 99%. Based on patient admission and discharge timing from medical records, the system matched over 95% of patients and provided precise identification of timing and duration of hypotensive episodes, hypoxemic events, tracheal intubation (by ETCO2 waveforms).

During an 18-month emergency intubation study, 98% of 850 patients continuous VS data were captured. Detailed VS analysis shows the rate of physiological adverse events associated with emergency intubation were oxygen saturation < 90% [25% of cases] and increase in heart rate > 20 bpm [22% of cases]. A detailed trauma resuscitation unit (12 beds) alarm study shows over 25,000 alarms were recorded per month (10% patient crisis, 30% patient warning, 26% patient advisory and 42% system warning alarms). Median alarm duration was 4 sec and 55.1% of total alarms were less than 5 second. Top three reasons for alarms are SpO2 Probe (23.4%), Tachycardia (6.1%) and Leads Fail (6.1%). In a 12 beds neuro trauma ICU , continuous auto collected VS (SBP,ICP,CPP) provides statistically significant prediction power for mortality, hospital and ICU length of stay, discharge GCS and 3 Month GOSE.

Conclusions: The trauma center wide system was reliable and provided a continuous record of events, because there were very few gaps in data collection. The system allowed automated documentation of patient care during time critical trauma patient reception and resuscitation, OR management and unusual events. Multivariable logistical regression of these data and linking with outcome could be used for Quality Management, teaching and health services research. Decision support algorithms and outcome predictions may be improved with such previously underutilized continuous vital signs data. Live ICU VS viewer with 2-D Shock and Brain Trauma Index display may enhances the situation awareness in real time.

CSF Levels of NSE and S100B in Patients with Severe TBI: Correlation with Clinical Measures

Background: Management of traumatic brain injury (TBI) focuses on mitigating against secondary insults, such as edema and ischemia. Both neuron-specific enolase (NSE) and S100-beta (S100b) are well-known markers of brain injury. Several studies have suggested correlation with outcome following severe TBI. We sought to determine the association of NSE and S100b with the traditional clinical markers of severity and poor outcome; low cerebral perfusion pressure (CPP), intracranial hypertension (ICH), and cerebral hypoxia.

Methods: Patients with head AIS>3, age>14, "isolated" TBI, need for intracranial pressure (ICP) monitor, and injury deemed survivable were prospectively enrolled. CSF was collected within 24 hours of injury and twice daily for 7 days and analyzed by ELISA.

Results: NSE and S100b concentrations in 100 CSF samples were matched with clinical variables recorded for each 12 hour period. Enrolled patients had a mean age of 35.8 ±15.1. 77.8% were male. Mean head AIS was 4.3 ±0.5 and admission GCS was 5.2 ±2.0. Maximum ICP and minimum CPP were not significantly associated with NSE or S100b levels. Duration of ICH (% of time ICP>20) was found to correlate with NSE levels (Figure 1). Degree of cerebral hypoxia, measured by brain tissue oxygen partial pressure (PbO2), was correlated with increased S100b levels (Figure 2).

Conclusions: Both NSE and S100b were associated with clinical measures of TBI severity. Further investigation is needed, but these markers of neuronal cell death demonstrate great promise as future targets of therapeutic interventions.

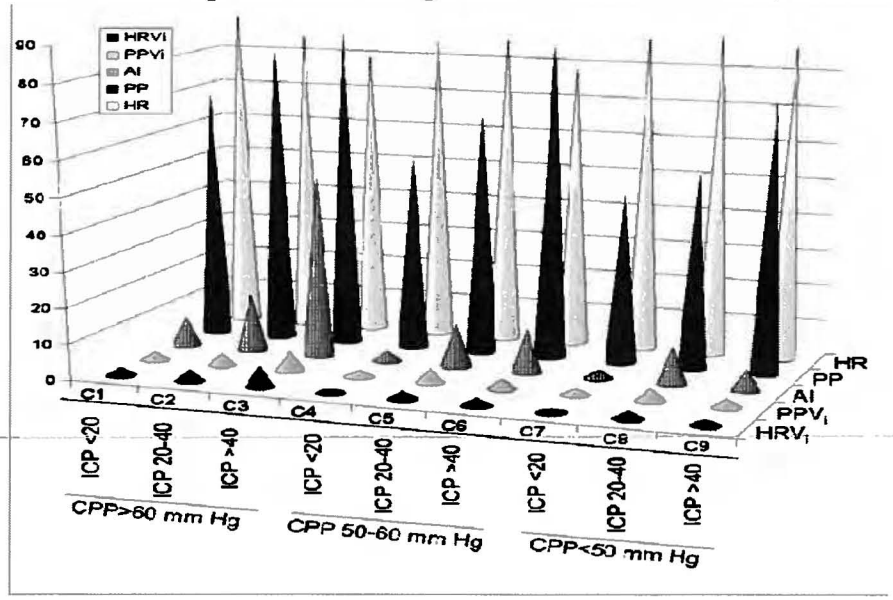
Heart Rate Variation Is Associated With Intractable Intracranial Hypertension And Cerebral Hypoperfusion

Introduction: Heart rate variability (HRV), intracranial pressure (ICP) and cerebral perfusion pressure (CPP) may be linked but specific relationships have not been established. Integer heart rate variability (HRVi) correlates well with standard spectral analysis and permits extended monitoring periods.

Hypothesis: We tested the hypothesis that continuous HRVi monitoring predicts intracranial hypertension and cerebral hypoperfusion as well as mortality and functional outcome after severe traumatic brain injury (TBI). We also evaluated the diagnostic and prognostic potential of continuous 'Autonomic Index' (AI=HRVi times PPVi) monitoring.

Methods: Dense integer data collected during continuous automated ICU monitoring for periods of 1 to 11 days on 25 patients admitted to our level 1 trauma center after severe (TBI) (Glasgow Coma Scale <9). 1,715,000 data points were available for a mean 106±62 hours.

Results: Dense integer data collected during continuous automated ICU monitoring for periods of 1 to 11 days on 25 patients admitted to our level 1 trauma center after severe TBI.1,715,000 data points were available for a mean 106±62 hours. With CPP>60 mmHg, PP, HRVi and PPVi increased significantly in response to increasing ICP ($p<<0.001$) while CPP <60 mmHg and PP<50 mmHg, even in the absence of ICH, was associated with a significant depression of HRVi and PPVi ($p<<0.001$) (Figure 1). ICP up to 40 mmHg still evoked a significant increase in HRVi and PPVi ($p<<0.001$), but CPP<50 mmHg accompanied by ICP>40 mmHg, was associated with suppression of both HRVi and PPVi. Mean HRVi, PPVi and AI predicted in-hospital mortality (sensitivity of 67%, specificity of 91-100%) as well as mean ICP and CPP. Percentage time of AI score <0.5 best predicted the long term functional outcome (AUC: 0.84 ± 0.08).



Conclusions:HRVi and PPVi can provide useful prognostic information in patients with severe TBI, particularly when combined as the AI score.

Critical Care Monitoring in the Field: Pre-Hospital Continuous Vital Signs Acquisition Identifies Best Predictors of Life-Saving Interventions in Trauma Patients

Introduction: Triage errors occur in a significant number of trauma patients. Vital signs (VS) data collected in pre-hospital care and recorded in trauma registries (TR) are often missing or unreliable.
Hypothesis: This paper tested the hypothesis that passively recorded VS predict life-saving interventions (LSI) and need for trauma center care better than use of retrospectively compiled TR VS data.
Methods: After IRB approval, 6 EMS helicopters were equipped with a Vital Signs Data Recorder (VSDR) to capture continuous VS from the patient onto a handheld PDA. Pre-hospital LSI's and those carried out within 2 hours after arrival in the trauma resuscitation unit (fluid bolus, CPR, drugs, intubation, transfusion etc) were considered outcome variables. A multivariate analysis was performed to determine which VS variables best predicted LSI's using the values in the TR and the VSDR
Results: Pre-hospital VSDR data were collected in 177 patients. There was significant difference for the highest and lowest heart rate, systolic blood pressure (SBP), oxygen saturation between the VSDR and the TR data ($p<0.001$). VSDR heart rate (>120) and oxygen saturation (<90%) predicted LSI's while none of the TR VS did so in a multivariate model. The area of the ROC for the VSDR data was 0.84 in the model which was validated by bootstrapping. VSDR and TR data showed that SBP was not an independent predictor of LSI.
Conclusions: Automated VSDR data showed tachycardia and desaturation (not captured in the EMS run-sheet and TR) as best predictors of LSI and, therefore, need of trauma center care. Continuous automated vital signs acquisition may lead to development of better trauma prognostic models and reduce triage errors

Cerebrospinal Fluid Levels of Inflammatory Mediators: Association with Outcome Following Severe Traumatic Brain Injury

Introduction: In patients with severe traumatic brain injury (TBI), the primary insult occurs at the time of initial trauma. The outcome following severe TBI is known to be associated with not only the severity of the primary insult, but the magnitude of secondary injury caused by an exceptionally complex interplay of numerous factors including neuroinflammation. There are a number of inflammatory mediators that are thought to play a part in secondary injury following severe TBI. The role of these mediators and the effect of this inflammatory process on outcome, however, are relatively poorly understood.

Hypothesis: This pilot study was undertaken to determine the feasibility of measurement of inflammatory mediators in cerebrospinal fluid (CSF) over time and investigate the relationship of these mediators with outcome in patients following severe TBI.

Methods: Patients at the R Adams Cowley Shock Trauma Center were prospectively enrolled over a 10-month period. Inclusion criteria were: age >14, admission within the first 6 hours after injury, Glasgow Coma Scale (GCS) <9 on admission, isolated TBI, and placement of an intraventricular catheter (IVC). CSF was drawn on admission and every 12-hours for 7 days. CSF concentrations of interleukin-1ß (IL-1 ß), IL-6, IL-8, tumor necrosis factor-□ (TNF□), IL-10, and IL-12 (p70) were analyzed using the Luminex® 200™ System (Luminex Corporation, Austin, TX) and the Milliplex™ Human Cytokine Immunoassay (Millipore Corporation, Billerica, MA). All samples were run in duplicate. Outcome was determined by the Extended Glasgow Outcome Score (GOSE) at one year following injury by an experienced trauma clinical research coordinator. GOSE 1-4 was defined as "unfavorable or poor functional outcome" and GOSE 5-8 as "favorable or good functional outcome." Student's *t* test was used to compare means based on continuous data. A p value of less than 0.05 was considered significant for all tests.

Results: Nine patients were enrolled in this pilot study over 10 months. As predicted by the inclusion criteria for this study, this cohort of patients was severely injured and neurologically compromised on admission. There was one in-hospital death from transtentorial herniation and progression to brain death. GOSE follow-up was completed for the 8 surviving patients at 3 months, but one patient was lost to follow-up after that interview, leaving 7 patients with 6-month and 1-year functional evaluations with GOSE. Two patients had significant functional improvement between the 6 month and 1 year follow-up periods.

Elevated levels of cytokines were found in the CSF of all patients over published norms. Marked elevation of IL-6, IL-8, and IL-10 levels were found. Overall low levels of IL-1 ß, TNF□, and IL-12 were detected.

Differences in mean admission levels of IL-6 and IL-8 between study subjects with good vs. poor outcome trended toward significance . Mean peak levels of IL-8 over the first week of admission were significantly different and mean peak IL-6 levels trended toward significance. There were no differences found in mean admission or mean peak levels of IL-1 ß, TNF□, IL-10, or IL-12. Traditional predictors of poor outcome such as admission GCS, Marshall Classification scores, and Head Abbreviated Injury Severity (AIS) Score wee no different between study subjects with good vs. poor outcome.

There were marked differences in mean levels of IL-6, IL-8, and IL-10 over time between patients with good and poor outcome. Different patterns in cytokine levels over time were also noted.

Conclusions: This preliminary analysis demonstrates that in patients with severe TBI, inflammatory mediators are detectable in the CSF at high concentrations and in varying patterns over time. IL-6 and IL-8 seem to be particularly promising as indicators of poor outcome. The precise role of these inflammatory mediators; whether they are causative of secondary injury or whether elevated levels are simply a marker of worse injury, is the focus of further investigation. The association between levels of these mediators and outcome has significant implications for the role of inflammatory system manipulation in the treatment of severe TBI.

CPP/ICP Dose Index: Dynamic 3-D Scoring in the Assessment of TBI

Abstract: Intracranial pressure (ICP) and cerebral perfusion pressure (CPP) data are essential for guiding therapy in severe traumatic brain injury (TBI) patients. We developed algorithms to process the continuous, high frequency digital ICP and CPP recordings of severe TBI patients so that they may be better monitored through automated data collection and decision support for therapeutic management. We tested a CPP/ICP "dose" (pressure*time) index and demonstrated a high predictive power for unfavorable outcome.

Introduction: Increasingly patient monitoring data is available in real-time from the hospital intranet. Algorithms to process such data for display and decision support purposes are needed to add value to patient care. In the case of TBI patients, development of a method to better estimate the critical dose of secondary injury after TBI is required[1]. In contrast to calculations of frequency or duration of episodes of ICP and CPP above treatment thresholds, pressure*time dose calculation takes into account two dimensions (the extent and the duration) of the insult. Dose calculations were shown to be a good measure of the scope of secondary brain injury after TBI[2]. We tested a CPP/ICP dose index as a way to process continuous digital data. Cumulative doses for both ICP and CPP above treatment thresholds (ICP>20 and CPP <60) were calculated, along with CPP/ICP dose index (<3). The latter takes into account three dimensions (the extent of intracranial hypertension and hypoperfusion with the duration) of the insult, being abnormal when at least one measure is excessively above the treatment thresholds if not both. We evaluated the value of cumulative ICP and CPP dose and dose index measurements for assessment of TBI patients throughout therapy.

Methods: We retrospectively analyzed the prospectively collected data of 27 severe TBI patients with Glasgow Coma Scale (GCS) <9, requiring ICP monitoring. Continuous digital recordings of ICP and CPP at 6 sec time intervals were acquired via a Trauma Center-wide vital signs data collection network. Potential artifacts were cleaned by a moving median with a window-size of 5 data points (30 sec). Mean values were then calculated over 5 min. We computed cumulative pressure*time doses of ICP>20, CPP <60 mmHg thresholds and CPP/ICP dose index <3 for the total ICP monitoring period, and compared their prediction power for three unfavorable outcome measures (28-day mortality, discharge GCS<13 and 3-month Extended Glasgow Outcome Scale (GOSE) <5) using receiver operating characteristics (ROC) methods.

Results: Twenty seven subjects yielded a total of 2890.6 hrs of data (1,734,374 data points). The CPP/ICP<3 dose showed consistently higher prediction value for all outcome measures, reaching to significance when compared to ICP>20 dose for predicting mortality (p=0.005).

Conclusion: Cumulative CPP/ICP dose index by processing continuous digital data demonstrated high predictive power for unfavorable outcome in severe TBI. Future research is warranted to evaluate the significance of different index limits.

Computerized patient vital signs charting method enhances real-time record keeping in ICU

Abstract: Computerized collection of real-time patient monitoring records may provide timely access to high frequency data in comparison with manual chart recordings. However, potential artifacts may require clinical judgment to recognize. In an analysis of 2.882 end-hour vital sings (VS: heart rate, oxygen saturation systolic/mean/diastolic blood pressure and temperature) recording of nine ICU patients, computerized VS data collection was found to be more accurate than manual recordings.

Introduction: Traditional practices of clinical vital signs (VS) documentation in the Intensive Care Unit (ICU) rely nurses to visually observe and manually record each hour or longer of patient vital signs onto the patient chart. Such charting may have the advantage of keeping nurses informed of VS, but it increases their already high workload. VSs were found to be often poorly documented in the period before adverse events[1]. The potential valuable information from high resolution of beat-to-beat VS is lost with manual documentation of once per hour or longer. Moreover, computerized data may be processed to support real-time clinical decision making. We assessed the accuracy of continuously recorded VS from patient monitors (C_VS) against manual VS (M_VS).

Methods: An ICU based VS collection network was used to collect VS from GE-Marquette Solar 7000/8000 monitor every 6 seconds. A cleaning algorithm was used by a moving median with a window-size of 5 data points (30 sec). Mean values were then calculated over 5 min for the following VS: Heart Rate (HR), oxygen saturation (SpO2), Intra-arterial Systolic / Mean/ Diastolic blood pressure (SAP/MAP/DAP) and temperature (Temp). The end-hour 5 min mean values were selected to compare with manual recorded end-hour VS (M_VS) data of the patient chart. The difference of M_VS and C_VS was calculated as a VS quality index (VSI) =| (M_VS-C_VS)/ [(M_VS+C_VS) *0.5]|. Two subject matter experts (SME) independently assessed those data points that had large VSI (Category B; defined as VSI >5% for HR, SAP, DAP, MAP and Temp and >1% for SpO2) to judge whether the C_VS or M_VS better reflected the patient status. A third SME acted as a tie-breaker. Category A VSI (VSI<=%1 for SpO2 and <=%5 for other VS) was accepted as insignificant.

Results: A total of 1,729,200- 6 second VS records (9 ICU patients on 3 days each) were analyzed to produce 2,882 end-hour C_VS records with matching M_VS. 76%-100% of Vital Signs pair (M_VS, C_VS) with small VSI (Category A). When VSI were large, (Category B) the SMEs judged that C_VS data were significantly more accurate estimate of patient VS (84%-93% p=0.0001) (Table1).

Conclusion: Computerized real-time VS data collection has a great potential for enhancing patient records that might be useful for both clinical and research purposes, besides saving nursing effort for patient care.

Is there Added Value in Continuous Vital Signs and Video Collection linked to Trauma Patient Outcomes?

Abstract: Patient record keeping in dynamic health care domains, such as trauma resuscitation, is plagued by inaccuracies due to the dual requirement for time-critical patient care and documentation. An automated continuous vital signs and video data collection system was evaluated and found to be reliable, with utility for Quality Management, teaching, as an event marker and in future, potential for decision- support and telemedicine applications.

Introduction: Emergency, time-critical, unusual and routine medical events recalled for health services research, debriefing conferences (Mortality & Morbidity) or for teaching are inaccurate due to hindsight bias, erroneous event sequencing, errors in timing and manual transcription of data. Linking such events to outcome requires laborious and time consuming chart review. We evaluated the utility and reliability of a hospital wide automated continuous vital signs and video network linked to patient outcomes as an event marker, teaching tool, and quality management (QM) record.

Methods: Patient vital signs (VS) monitors (GE-Marquette-Solar-7000/8000) were networked in a major trauma center including 12 trauma resuscitation areas (TRU), 6 operation rooms (OR), 9 post anesthesiology care beds (PACU) and 36 ICU beds. Dedicated 24x 7 continuous real-time collection of VS trends and waveforms occurred for each patient monitoring location (TRU/OR/PACU/ICU). These data were compressed and transferred to a centralized server through the hospital secured intranet where they were archived. A multi-user based data decoder, viewer and analyzer was developed for VS data abstraction, artifact removal, 5min-60 min selectable averaging, and summary data output to both text and MS-Excel format. The server was interfaced directly with Trauma Registry queries to provide over 100 patient-specific demographics and outcomes. Video, recorded continuously from all TRU's, and OR's, was stored in a 72 hour buffer before being automatically overwritten (like hospital security cameras), so minimizing HIPPA issues. Selected videos were abstracted for QM and teaching conferences or for approved research protocols.

Results: During 12 months over 80-VS variables were collected including waveforms electrocardiogram, oxygen saturation, end-tidal carbon dioxide, (ECG/SpO2/CO2/Respiration) and numerical values every 6 seconds of heart rate, blood pressure, intracranial pressure, cerebral perfusion pressure, respiratory rate, temperature, (HR/BP/SpO2/ETCO2/ ICP/CPP/RR/TEMP etc) at 240Hz. Data collection averaged 76.4 KB/hour for numerical and 12.3MB/hour for waveforms. Over 15,000 days (41 patient-locations*365days=14,965 days) of over 8,000 patients VS were collected with system uptime of over 99%. Based on patient admission and discharge timing from medical records, the system matched over 90% of patients and provided precise identification of timing and duration of hypotensive episodes, tracheal intubation (by ETCO2 waveforms) and hypoxemic events. Video clip review became the standard of choice for Trauma Fellow conferences and Human Factors based research efforts (www.hfrp.umm.edu). Specialized ICU monitoring, e.g. of head-injured patients, validated continuous CPP as a predictor of outcome, showed events causing elevation in ICP and provided QM markers (e.g. hyperventilation status).

Discussion: The multi-media hospital wide system was reliable and provided a continuous record of events, because there were very few gaps in data collection. The system with video, allowed automated documentation of patient care during time critical trauma patient reception and resuscitation, OR management and unusual events. Multivariable logistical regression of these data and linking images with outcome are powerful QM, teaching and health services research tools. Decision support algorithms and predictors of outcome developed from these analyses may improve patient care, while the ability to capture these data in real-time will facilitate future medical consultation and telemedicine applications.

Real-time patient Vital Signs Data Registry for Trauma Patient Care

Introduction: Continuous display of patient physiological data is standard anesthesia practice; recording, retrieval and processing of such data is not. In time-critical, multi-tasking domains requiring life-saving interventions, documentation is sparse. We evaluated reliability of an automated vital signs collection system and tested proof of concept for 24x7 retrospective construction of events and prospective prediction of patient outcome

Methods: Real-time patient vital signs data feeds from monitors (GE-Marquette-Solar-7000/8000) were networked in a major trauma center to include 12 bed trauma resuscitation unit (TRU), 6 operating-rooms (OR), 9 post-anesthesia and 36 intensive care beds. Real-time vital signs waveforms, trends and alarms were compressed and transferred to a centralized server through the secured hospital intranet and archived. Custom processing and viewing programs were developed for patient data abstraction, artifact removal, 5-60 min time window averaging, and summary data output to both text and MS-Excel format (Figure). The server was interfaced with the CERNER to allow viewing of patient records and directly with Trauma Registry queries to provide over 100 patient-specific demographics and outcomes.

Results: During 12 months over 80 variables were collected including continuous electrocardiogram, oxygen saturation, end-tidal carbon dioxide (ECG/SpO2/CO2/Respiration) waveforms and numerical values every 6 seconds of heart rate, blood pressure, intracranial pressure, cerebral perfusion pressure, respiratory rate, temperature, (HR/BP/SpO2/ETCO2/ICP/CPP/RR/TEMP etc) at 240Hz. Data rates after compression averaged 76.4 KB/h for numerical and 12.3MB/h for waveforms. Over 20,000 days (64 patient-locations*365days= 23360 days) of over 8,000 patients vital signs were collected with system uptime > 99%. Based on patient admission and discharge timing from medical records, the system matched over 90% of patients and provided precise identification of timing and duration of hypotensive episodes, hypoxemic events, tracheal intubation (by ETCO2 waveforms). 100% of 384 TRU intubation data were captured in a 6-month data collection period. Specialized monitoring, e.g. of 27 Glasgow Coma Scale < 9 head-injured patients, validated continuous CPP as predicting mortality.

Conclusions: The trauma center wide system was reliable and provided a continuous record of events, because there were very few gaps in data collection. The system allowed automated documentation of patient care during time critical trauma patient reception and resuscitation, OR management and unusual events. Multivariable logistical regression of these data and linking with outcome could be used for Quality Management, teaching and health services research. Decision support algorithms and outcome predictions may be improved with such previously underutilized continuous vital signs data.

High Resolution ICP and CPP Data Better Predict Outcome of Severe TBI

Background : Manual end-hour intracranial pressure (ICP) and cerebral perfusion pressure (CPP) documentation is the prevalent practice, even in dynamic patients. We assessed the impact of artifacts on accuracy and utility of real-time high resolution automated ICP and CPP recordings by comparing with manual documentation and evaluating its correlation with outcome in severe traumatic brain injury (TBI).

Methods : After IRB approval, 30 patients with severe TBI with admission Glasgow Coma Scale (GCS)<9, requiring ICP monitoring were included in the study. Real-time recordings of ICP and CPP were acquired automatically at 6 sec intervals via a Trauma Center-wide vital signs data collection network. Potential artifacts were cleaned by moving median with a window-size of 5 data points (30 sec). 5 min mean values were then calculated for 4.6±2.6 days. The extent and duration of ICP>20mmHg and CPP<60mmHg were calculated as pressure-time dose (PTD: mmHg*h) by using either automated (PTDa) or manual (PTDm) recordings. Bland-Altman plot was used to assess the agreement of PTDa and PTDm. Prediction values for in-hospital mortality and long term functional outcome (Extended Glasgow Outcome Scale; GOSE) were calculated using receiver operating characteristics (ROC) methods. Spearman rank correlation test was used to establish the correlation between PTD values and discharge GCS, length of ICU stay (LOS_ICU) and length of hospital stay (LOS_H).

Results : Thirty subjects (27 men, 3 women) yielded a total of 3296 hrs of data. Bland-Altman plots demonstrated general agreement between PTDa and PTDm with a mean bias of -3.8 for ICP (95% confidence interval: CI from -13.9 to 6.3) and -10.9 for CPP (95% CI from -0.2 to 22.1). PTDa and PTDm for ICP were significantly higher in patients with unfavorable outcome (GOSE≤4) than in patients with favorable outcome (GOSE>4) (p=0.0004 and p=0.01, respectively). However, for CPP where Bland-Altman plots showed the highest mean bias, PTDa but not PTDm showed significant difference between patients with favorable vs. unfavorable outcome (p=0.003 and p=0.053, respectively). Both PTDa and PTDm had high predictive power for functional outcome and in-hospital mortality (Table 1). Both PTDa and PTDm values for ICP and CPP were strongly correlated with LOS_ICU (p=0.009 and 0.007 vs. p=0.005 and 0.006, respectively), LOS_H (p=0.009 and 0.005 vs. p=0.001 and 0.005, respectively) and discharge GCS scores (p=0.008 and p=0.038 vs. p=0.042 and p=0.015, respectively).

Conclusion : PTD calculation of real time, high resolution ICP and CPP recording is less labor intensive than manual recording and showed better correlation with clinical outcomes. This technique should be the standard for future studies of severe TBI.

Pressure-time dose of automated ICP and CPP data predicts outcomes in severe TBI

Background: Intracranial pressure (ICP) and cerebral perfusion pressure (CPP) measurements are the primary basis for the care of the severe traumatic brain injury (TBI) patients. We tested the accuracy of a pressure-time dose (PTD: mmHg*h) based on automated ICP and CPP data in predicting outcomes of severe TBI patients.
Methods: ICP and CPP data for 30 severe TBI patients were collected automatically at 6 sec intervals. PTDs of ICP and CPP over or under two different thresholds were calculated for early stage (Emergency Department stay: 3.4=/- 2.8 h) and total stay (4.6 +/- 2.6 d). Four outcomes (mortality, 3-month Extended Glasgow Outcome Scale -GOSE, discharge GCS and decompressive craniectomy) were used in assessing prediction value of PTDs.
Results: Total stay PTDs were strong predictors of GOSE and mortality (Fig.). In particular, early stage PTDs for ICP thresholds had 100% sensitivity but low specificity (17-47%). Total stay PTD of ICP>20mmHg correlated with discharge GCS (p=0.016), and PTD of ICP>30mmHg correlated with the need for decompressive craniectomy (p=0.03).
Conclusion: Dose-based scoring of continuous automated ICP and CPP recordings seems to be a strong predictor of outcomes in TBI. Direct management of dose-based scoring at early stages might be valuable in therapeutic decisions.

Summary of Staff, Roles and Percent Effort by Project/Sub-project

STAFF MEMBER	ROLE	% EFFORT (%FTE)
Thomas Scalea	PI	2.5
Lisa Gettings	Administrator	0
Karen Murdock	Project Manager	55
Colin Mackenzie	Sub-Project PI; Vital Signs study	20
Peter Hu	Co-Investigator	41.5
Yan Xiao (resigned)	Technical Support	0
Steven Seebode	Technical Support	57.4
Eric Lund	IT Application Engineer	75
Deborah Stein	Sub-project PI; Cytokine study	8.4
Bizhan Aarabi	Co-Investigator	2
Richard Dutton	Co-Investigator	0
Allison Lindell	Coordinator; Cytokines study	41.5
Kaspar Keledjian	Cytokine technician	20
Robert Rosenthal	Sub-project PI; Animal model	7.3
Gary Fiskum	Co-Investigator	27.5
Karen Volpini	Database Management	0
Madeline Mitrou	Research Nurse	28.3
Yawei Wang	Research Nurse	51.9
Amechi Anozado	Research Assistant	59
Margaret Mensa	Research Nurse	31.9
Diane Rouse	Research Nurse	42.2
Marianne Hattan	Research Nurse	80.8
Keri Volpini	Research Assistant	29.7
Christine Wade-Mariani	Research Assistant	0
Charles Simpson (resigned)	Research Assistant	0
Scott Berry (resigned)	Research Assistant	0
Tondeleyo Gonzalez	Research Assistant	17.9
Carrie Sauer (resigned)	Research Assistant	0
Olga Kolesnik	Research Assistant	81
Sean Jordan (resigned)	Research Assistant	0
Sara Wade	Research Assistant	55.7
David Prakash	Research Assistant	89.8
Ryan Gens (resigned)	Research Assistant	0
Cris Imle	Physical Therapist	33.4
Myra Collins (resigned)	Research Assistant	3.8

Jonathan Gooch	Research Assistant	52.4
Genna McFarland	Student Assistant	80.3
Kristina Clem (resigned)	Data Entry	0
Joe Kufera	Statistician	20.4
Gordon Smith	Epidemiologist	0
Julie Hazleton	Technician	0
Jennifer Racz (resigned)	Technician	50
Xiaoli Xiao (resigned)	GRA	0
Wei Xiong	GRA	100*
Keng-Hao Liu	GRA	100*
Yu Wei Chang (resigned)	Data Processor	100
Ryan Seebode	Data Entry Assistant	100
Susanna Scafidi	Co-Investigator	0
Matthew Woodford	Post-doctoral Fellow	100
Rao Gulliapalli	Co-Investigator	8.7
Matt Lissauer	Co-Investigator	8.5
Jiachen Zhuo	Post-doctoral Fellow	50
Josh Ayres	Student Assistant	68.8

* 100% effort for a GRA is 20 hours/week

Contract Expenditures to Date

COST ELEMENTS	THIS QUARTER	YEAR 3 TOTAL	YEAR 2 TOTAL	YEAR 1 TOTAL	PROJECT CUMULATIVE TOTAL
Personnel	$207,672	$1,121,210	$1,239,701	$477,416	$2,838,327
Fringe Benefits	$29,623	$178,018	$217,915	$75,619	$471,552
Supplies	$25,199	$123,776	$58,499	$18,363	$200,638
Equipment	$25,249	$37,146	$14,898	$22,125	$74,169
Travel	$1,310	$4,813	$3,330	$1,578	$9,721
Other Direct Costs	$7,590	$20,433	$18,145	$2,070	$40,648
Subtotal	*$296,642*	*$1,485,395*	*$1,552,487*	*$597,171*	*$3,635,054*
Indirect Costs	$70,750	$374,916	$399,045	$149,512	$923,473
Fee	$0	$0	$0	$0	$0
Total	$367,392	$1,860,311	$1,951,533	$746,683	$4,558,527

*Includes expenditures through 9/30/10